

### **REMARKS**

The Office Action has indicated that applicants have successfully overcome the 35 U.S.C. §112, second paragraph, rejection previously imposed. The Examiner is thanked for withdrawing the previously imposed rejections. In the Office Action dated September 9, 2003, Claims 28-37 were rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Further, Claims 19, 28 and 29 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 20-27 were objected to as they depend from Claim 19.

The Examiner is respectfully requested to withdraw the rejection in view of the reasons, arguments and evidence presented herein below.

Before addressing the merits, it is to be noted that Applicants have amended Claim 24 by inserting "The" at the beginning of the sentence so that it is grammatically correct. In addition, Claim 28 has been amended to change the term "dysfunction" with the equivalent term "disorder". The term "disorder" is synonymous with dysfunction, as indicated by the enclosed definition of "disorder". (See attachment hereto.) As defined, disorder is something that disturbs the normal or regular function, while dysfunction is defined as impaired or abnormal functioning. Thus, the term "dysfunction of the circulatory system" herein is being used synonymously with the term

“disorder of the circulatory system”. Moreover, one of ordinary skill in the art reading the application would construe the term “dysfunction of the circulatory system” to be a disorder of the circulatory system. Even the United States Patent and Trademark Office understands it as such, as it characterizes the methodology therein as treatment of circulatory disorders”. See page 7 of the Office Action, second paragraph. Further, the term “disorder” is also utilized in the instant application. For example, on page 2, line 29, the application refers to vascular disorders and on page 3, lines 10-15, it characterizes the use of the S-nitrosothiol derivatives for the treatment of “disorders” of the circulatory system. Claim 28 has been amended to redefine the amount utilized as the amount effective to treat the “disorder of the circulatory system”. Claim 29 has been amended to define the amount utilized in the pharmaceutical composition as “effective”. These aforementioned amendments do not narrow the scope of the claims.

Claim 38 has been added and is directed to the use of the compound of Formula II for the treatment of a disorder of the circulatory system. Support is found on page 4, lines 9-15 and page 1, lines 5-11 and page 3, lines 15-16 of the instant application.

No new matter has been added to the application.

With regard to the 35 U.S.C. §112, first paragraph rejection of Claims 28-37, the Examiner stated the claimed subject matter is enabling for in vitro testing, but questioned the *in vivo* utility, citing various references which, according to the Examiner, provide instances where the use of ACE inhibitors for treating cardiovascular diseases produced unpredictable results.

In traversing the rejection pursuant to 35 U.S.C. §112, first paragraph, Applicants note that the Office Action is basing its arguments on compounds which are totally unrelated to the compounds described in the present application and which, therefore, have no bearing on the question of utility of the compounds of the present invention. It is incumbent upon the Patent and Trademark Office, whenever a 35 U.S.C. §112, first paragraph, rejection is made, to explain why it doubts the truth or accuracy of any statements in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *See In re Marzucchi* 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 CCCPA (1971). Here, the Office Action has not provided any evidence which specifically refutes the pharmaceutical utility of the compounds of the present invention. Thus, the United States Patent and Trademark Office has not made out a prima facie case of non-enablement.

However, to advance prosecution of the application and in support of Applicants' position of the patentability of Claims 28-37 of the instant invention, Applicants submit concurrently herewith an executed Declaration Under 37 C.F.R. §1.132 by one of the inventors, Jose Repolles Moliner, the contents of which are incorporated by reference.

The declarant in the Declaration has conducted several *in vivo* experiments utilizing art recognized tests, which show that the compounds of the present invention exhibit *in vivo* therapeutic efficacy in treating representative cardiovascular dysfunctions, such as thrombotic disorders and hypertension. For example, the data presented in the show the anti-thrombotic effect of representative S-nitrosothiols of the present invention in several *in vivo* tests, as well as the effect on bleeding time *ex vivo*, the results of which

are tabulated in Tables 1-3 in the accompanying Declaration. The data presented also demonstrate the *in vivo* hypotensive effect of representative S-nitrosothiols of the present invention, the results of which are tabulated in Table 4, in the accompanying Declaration. The data presented is that of representative examples of the present invention. As shown by the data, and the accompanying Declaration, the claimed subject matter clearly exhibits *in vivo* pharmaceutical utility and is useful for treating circulatory dysfunctions. Consequently, the rejection of Claims 28-37 under 35 U.S.C. §1.112, first paragraph, has been overcome. Withdrawal thereof is respectfully requested.

With regard to the 35 U.S.C. §112, second paragraph rejection of Claims 19, 28 and 29, Applicants offer the following comments.

Specifically, the Office Action stated that Claim 28 is drawn to a method of treating “circulatory disorders”, and claims 29-37 are drawn to a “pharmaceutical” composition. The Office Action rejected Claim 28 for use of the term “dysfunctions of the circulatory system”, alleging that it is indefinite and ambiguous.

Applicants respectfully traverse the rejection on several grounds. First, the term dysfunction of the circulatory system is a well-recognized term to one of ordinary skill. (See, Declaration of Jose Moliner, Paragraph 28.) Moreover, as indicated above, it is used synonymously with disorder. Further resort to standard dictionaries and treatises in the art also clearly establish what is meant by the term. For example, “Diseases and disorders of the Circulatory System” is a Major Diagnostic Category (MDC) in the Diagnosis Related Groups (DRGs), a diagnosis classification system used for healthcare reimbursement by health plans and Medicare. In standard textbooks of medicine, including Harrison’s Principles of Internal Medicine, 15<sup>th</sup> ed., McGraw Hill,

New York, 2001, the Table of Contents at p. xiv refers to illnesses of the cardiovascular system as “Disorders of the Cardiovascular System.” Thus, as used in the specification, one skilled in the art understands that the term, “disorder of the circulatory system”, is defined as a problem or fault in the circulatory system.

/ It is to be noted that nitric oxide plays an important role in the pathophysiology of the cardiovascular system. The role of nitric oxide as a signaling molecule is well established and has been recognized in the 1998 Nobel Prize in Physiology or Medicine to the Karolinska Institute. Within the cardiovascular system, nitric oxide regulates vascular tone, platelet function, leukocyte-endothelial and platelet interactions, cardiomyocyte function and plays an important role in cardiac electrophysiology. Nitric oxide also modulates apoptosis and hypertrophy.

Decreased levels of nitric oxide have been implicated in cardiovascular pathological conditions including, but not limited to: endothelial dysfunction, hypertension, pulmonary hypertension, atherosclerosis, thrombotic disorders, heart failure, stroke, ischemia and ischemia-reperfusion. Therefore, a nitric oxide donor releases nitric oxide and, thus, is useful for prevention and treatment of those cardiovascular pathological conditions.

In light of the broad implications of nitric oxide on cardiovascular function and the fact that “disorder of the circulatory system” is a term of art, it respectfully submitted that the term “disorder of the circulatory system” is a term that is clearly understood by one of ordinary skill in the art. Thus, this term in Claim 28 is not indefinite. Consequently, the rejection of Claim 28 under 35 U.S.C. §112, second paragraph is overcome; withdrawal of the rejection is respectfully requested.

The Examiner rejected Claim 19 for lack of antecedent basis.

Applicants have amended Claim 19 accordingly adding the word "an," in accordance with the suggestion in the Office Action. By this amendment, Applicants have obviated the objection to claims 20-27, which should now be in condition for allowance.

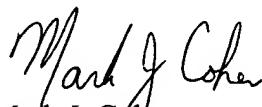
The Examiner rejected Claim 29 for use of the plural of the term "derivatives."

Accordingly, Applicants have amended Claim 29 changing "derivatives" to the singular form.

It is to be noted that the amendment to the claims described hereinabove do not narrow the scope thereof. Further, the amendments to the claims overcome the rejections thereof under 35 U.S.C. §112, second paragraph. Withdrawal thereof is respectfully requested.

For the foregoing reasons, Applicants respectfully submit that the rejection of all of the 35 U.S.C. §112 grounds for rejection have been overcome and that patentable subject matter has been presented. It is respectfully submitted that the present case is in condition of allowance, which action is earnestly solicited.

Respectfully submitted,



Mark J. Cohen  
Registration No. 32,211

Scully, Scott, Murphy & Presser  
400 Garden City Plaza  
Garden City, NY 11530  
(516) 742-4343  
MJC:MMR:rjl/lf/dg